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SULFONAMIDE MIXTURES AND COMBINATIONS

Sulfonamides have been largely replaced by antibiotics, but they are still of great value in the treatment of meningococcal meningitis, bacillary dysentery and many urinary-tract infections; they can also be used in place of penicillin for prophylaxis of rheumatic fever. Sulfonamides are offered singly and in mixtures of two, three, and even four or five different analogues.

The main reason for the use of the mixtures is that sulfonamides are independently soluble, while their antibacterial effects are additive. The risk of renal precipitation with high concentrations of any one sulfonamide is thus reduced. The risk is greatest with the sulfapyrimidines (sulfadiazine, sulfamerazine, sulfamethazine), all of which are poorly soluble at the usual pH of urine. The usefulness of a mixture of these three sulfonamides is officially recognized by its inclusion in the Pharmacopeia as Trisulfapyrimidines Oral Suspension and Tablets (167 mg. of each of the three analogues per teaspoonful or 500-mg. tablet).

EFFICACY AND ALLERGIC POTENTIAL - The reduced concentration of each component appears to be the only advantage of mixtures of different sulfonamides; a mixture has no greater antibacterial efficacy than an equivalent amount of a single sulfonamide. The evidence is conflicting as to the relative frequency of allergic reactions after multiple courses of mixtures and of the single components. (Because of its extremely high potential for causing such toxic and hypersensitivity reactions as fever and rash, the use of one sulfonamide — sulfathiazole — alone or in combinations, should be avoided.)

There are many mixtures of four or five sulfonamides, but the addition of other sulfonamides to Trisulfapyrimidines, USP offers no therapeutic advantage. In a word, the effectiveness of all mixtures of sulfonamides appears to be about the same as that of a single active sulfonamide such as sulfadiazine. The risk of renal crystalluria is greater with sulfadiazine than with the mixtures, but it is probably negligible if the fluid intake is high enough to maintain a urine output of at least 1200 cc. per day. High fluid intake is important even with the mixtures, however.

Sulfonamide combination drugs containing analgesics and antihistaminics are promoted for the treatment of common upper-respiratory infections. It is assumed that bacteria are important in such infections and that they can be controlled by the

sulfonamides present in the combination. However, most upper-respiratory infections are probably caused by viruses. Moreover, when significant bacterial infection occurs (as in streptococcal pharyngitis), penicillin or some other antibiotic active against the infecting organism is preferable to a sulfonamide. Aspirin or antihistamines can be prescribed separately if they are needed.

COMBINATIONS WITH PENICILLIN - Many combinations of sulfonamides with antibiotics, usually penicillin, are available. Claims that sulfonamides and penicillin in combination have synergistic or additive effects in infections caused by staphylococci, hemolytic streptococci, pneumococci and meningococci are not supported either experimentally or by controlled clinical trials. With the first three of these organisms (except for resistant staphylococcal strains), adequate doses of oral penicillins are almost always effective, and the inclusion of sulfonamides, which are much less active, does not make the combination more effective. Some clinicians believe that the combination of a sulfonamide and penicillin is more effective than a sulfonamide alone in meningococcal infections, but there has been little confirmation and some contrary evidence. The treatment of choice for meningococcal meningitis is Sulfadiazine Sodium Injection, USP, administered intravenously to give a serum level of 12 to 15 mg. per hundred cc., followed by Oral Trisulfapyrimidines, USP in dosages that maintain this serum concentration. If penicillin is also used, crystalline potassium penicillin G in doses of at least 10,000,000 units a day should be given parenterally.

Sulfonamide-penicillin combinations are sometimes used when a mixed upper-respiratory-tract infection is suspected. But when acute upper-respiratory infections are not entirely viral, a single bacterial organism such as streptococcus, pneumococcus or Hemophilus influenzae, is in most instances responsible, and penicillin alone or some other antibiotic should be used. In urinary-tract infections, penicillin's contribution is negligible. In a serious mixed infection, as in peritonitis or postoperative pneumonia, antibiotics appropriate for the infection should be chosen and employed parenterally.

OTHER COMBINATIONS - There is no convincing evidence for the usefulness of combinations of sulfonamides with erythromycin (as in Erythrosulfa [Upjohn], Erythromid [Abbott], and Ilosone Sulfa [Lilly]), or with tetracycline (as in Tetrex c T/S [Bristol] and Azotrex [Bristol]). For a large initial loading dose of sulfonamide, such a combination would provide an excessive amount of erythromycin or tetracycline. Moreover, if an infection is serious enough to require large doses of an antibacterial drug, the appropriate antibiotic alone should generally be used, and the sulfonamides, with their many deficiencies, should be omitted.

Valid indications for the choice of a sulfonamide in combination with other drugs are rare. When an oral sulfonamide is required for systemic infections, Trisulfapyrimidines, USP is preferred. For urinary-tract infections it is as effective and as safe as the relatively soluble single sulfonamides, sulfisoxazole (Gantrisin - Roche) and sulfisomidine (Elkosin - Ciba). Long-acting sulfonamides such as Sulfamethoxypyridazine, USP (Kynex - Lederle; Midicel - Parke, Davis) and sulfadimethoxine (Madribon - Roche) have the advantage of one-dose-a-day convenience, but the disadvantage of slow excretion when toxic-allergic reactions to sulfonamides appear.

TESTS OF DIGITOXIN TABLETS

Many seizures of substandard lots of Digitoxin, USP have been reported in the "Notices of Judgment" of the Federal Food and Drug Administration, and now laboratory tests of digitoxin tablets purchased from 35 drug companies show that the samples obtained from nearly a quarter of the companies failed to meet the requirements of the U.S. Pharmacopeia.

The analyses, performed for The Medical Letter by a qualified commercial laboratory, showed that all samples met the official requirements for identification and disintegration time, and that none exceeded permissible limits for weight variation of the tablets. Eight samples, however, contained either insufficient or excessive amounts of digitoxin per tablet (the Pharmacopeia limits are 90 to 110 per cent), or excessive amounts of other digitoxosides (up to 10 per cent is permitted by the U.S.P.). As shown by the table on p. 48, the maximum variation in digitoxin content was found to be nearly twice the tolerance, with a range of 80 to 117 per cent of the labeled content. The amount of "other digitoxosides" found ranged up to 15 per cent.

In rapid digitalization, the physician exercises continuous or frequent observation of the effect of the digitalis product on the patient so that it is clinically unimportant whether the product contains 85 per cent or 115 per cent of the labeled dosage. On maintenance therapy, however, a dosage that is 15 per cent less than prescribed could result in loss of digitalization effect, and a dosage of 15 per cent more could eventually cause digitalis intoxication. The most serious risk would occur if a patient maintained on tablets with a low digitalis content received tablets on his next prescription with a high content (or vice versa).

OTHER DIGITOXOSIDES - The Pharmacopeia permits an additional 10 per cent of digitoxosides other than digitoxin. The highest amount present in any of the samples tested was 15 per cent of the labeled amount of digitoxin. Since gitoxin, the principal impurity found in digitoxin, is not likely to be absorbed, the clinical significance of the excess of "other digitoxosides" is questionable.

In fairness to the companies whose samples were found to be substandard, it should be realized that with most drugs, no feasible control procedure can guarantee 100 per cent compliance with standards; another series of tests would almost certainly show a quite different set of results. As pointed out in previous Medical Letter reports, no one test report can provide a reliable guide to the quality of a company's products; but it is hoped that the cumulative results of a long series of tests of different drugs will provide such a guide.

Twenty-seven of the 35 samples tested did conform fully to the standards, and without doubt many of the smaller companies supplying digitoxin are reliable sources of the drug. Nevertheless, in view of the uncertainties and the special risks with this drug, the physician should probably prescribe the product of a particular company known to have good control procedures. The following table shows the results of the tests of digitoxin. All samples conformed to USP requirements with respect to identity, disintegration time (six tablets from sample disintegrated in 30 minutes) and weight variation (no more than two out of 20 tablets may vary

from average weight by 15 per cent and none by more than 30 per cent). The price shown is the price paid by the pharmacist per thousand 0.1-mg. tablets. Figures above or below USP limits (confirmed by duplicate determinations) are indicated by asterisks. The column "Other" shows the percentages of other digitoxosides.

Company	Digitoxin	Other	Price	Company	Digitoxin	Other	Price
Allen Pharmacal	100%	8%	$2.80	Lannett	*86%	*11%	$3.40
American Drug Prod.	92	9	1.90	Lilly (Crystodigin)	93	10	6.06
American Pharmaceutical	94	8	4.40	Massengill	99	6	5.00
Approved Pharm.	95	3	3.27	H. L. Moore Chem.	96	8	1.55
Bryant Pharm.	*87	7	3.30	Penhurst Pharm.	94	8	2.50
Carroll Chemical	96	8	2.30	Raway Pharmacal	*86	*11	1.65
Consolidated Midland	99	5	3.10	Robinson Labs.	100	9	2.50
Cowley Pharm.	97	6	3.10	Stanley Drug Prod.	*89	7	2.50
Robert Daniels	94	7	3.30	Success Chemical	101	8	3.75
DuMont Pharmacal	99	6	1.75	Supreme Pharm.	105	9	4.40
Evron	*85	*15	3.75	Testagar	95	10	6.60
Faraday Labs.	97	9	2.50	Upjohn	102	5	6.34
E. Fougera (Digitaline Nativelle)	94	8	13.50	Vita-Fore	99	9	1.75
				Vitamin Research	*80	*14	2.00
				Vitarine	105	5	3.90
Gotham Pharm.	*117	5	2.03	Wales Chemical	90	4	2.80
Harvey Labs.	94	*12	2.25	West-ward	100	9	3.50
Jan Labs.	99	8	1.70	Wyeth Labs. (Purodigin)	102	6	5.46
Kirkman Pharmacal	100	8	2.50				

THIST

Physicians who use the advertising blotters sent to them by Cole Chemical Co. may find on their desks an invitation to prescribe Thist; and information from pharmacists indicates that many physicians do. Thist depends largely on an ancient drug, strychnine, to "relieve that let-down feeling...during convalescence from influenza and other debilitating conditions." In addition to strychnine sulfate (1/100 gr.), each Thist tablet contains thyroid (1/20 gr.), zinc phosphide (1/10 gr.) and ferric pyrophosphate (2 gr.). The recommended dose is one or two tablets a day.

Although strychnine preparations have had long usage as tonics, there is no pharmacologic or therapeutic justification for such use. As an appetite stimulant the official strychnine preparation, Nux Vomica Tincture, NF is probably helpful only because of its alcoholic content. Zinc is considered a nutritional essential in some animals and perhaps in man; but a deficiency of zinc has never been observed in man, and there is no evidence that a supplement of zinc is of any value in accelerating convalescence. If there is an iron deficiency, the small amount of elemental iron in each tablet of Thist (16 mg.) is wholly inadequate; about 200 mg. daily is required for correction of iron deficiency anemia. The need for thyroid in post-infectious asthenia or debility has never been established; in true hypothyroidism, 1/20 gr. of thyroid, the amount in each Thist tablet, must be considered a placebo dose. Blotters are useful, but we doubt that Thist is.

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